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Short Versus Longer Antibiotic Duration for Community-Acquired Pneumonia

A Multicenter Target Trial Emulation

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Background: Shorter antibiotic courses for community-acquired pneumonia (CAP) may reduce adverse effects and resistance. However, real-world data supporting very short durations remain limited.

Objective: To evaluate the safety and effectiveness of 3- to 4-day versus 5-day or more antibiotic durations in hospitalized patients with CAP who achieve clinical stability by day 3 (afebrile, no new oxygen, and stable vital signs).

Design: Observational emulation of a target trial.

Setting: 67 Michigan hospitals between 2017 and 2024.

Patients: Adults hospitalized (non–intensive care unit) with CAP who received 3 days of antibiotics, were clinically stable by antibiotic day 3, and met the strict eligibility criteria of the Pneumonia Short Treatment trial.

Intervention: 0 to 1 additional days of antibiotic treatment versus 2 or more days of additional antibiotic treatment (that is, shorter [3 to 4 days] vs. longer [≥5 days] total antibiotic duration).

Measurements: The main outcome was 30-day all-cause mortality. Other outcomes included 30-day hospital readmission, urgent health care visits, and *Clostridioides difficile* infection.

Results: Among 55 517 hospitalized patients with CAP, 5620 (10.1%) ultimately met eligibility criteria for short-course therapy after comorbidity, clinical stability, and treatment duration criteria were applied. Median age of eligible patients was 68.2 years, and 54.3% were men. Median antibiotic duration was 7 days, with only 7.9% (444 of 5620) receiving 3 to 4 days. Thirty-day adjusted risk ratios for short- versus long-course antibiotic therapy were 0.89 for mortality (95% CI, 0.01 to 2.25), 1.07 for readmission (CI, 0.81 to 1.42), 0.94 for urgent visit (CI, 0.70 to 1.28), and 1.01 for *C difficile* infection (CI, 0.18 to 5.68).

Limitation: Few short-duration patients and potential residual confounding.

Conclusion: Only 10.1% of inpatients with CAP met the strict eligibility criteria for short-course therapy. The short- and longer-course antibiotic treatment groups had similar mortality rates, and there was little difference in benefits and harms.

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Community-acquired pneumonia (CAP) is the most common infectious cause of hospitalization (1). The mortality rate during hospitalization is 6.5%, with 1-year mortality rates of 30.6% (1). Emerging evidence indicates that shorter durations of antibiotic therapy for infections yield similar efficacy to longer durations while reducing adverse effects and carrying a lower risk for producing antibiotic resistance (2–10). Thus, the updated 2025 American Thoracic Society CAP guidelines now state that "for adult inpatients with nonsevere CAP who reach clinical stability, we suggest less than 5 days of antibiotics rather than 5 or more days of antibiotics" (11). This update was partially due to the 2021 Pneumonia Short Treatment randomized clinical trial of hospitalized patients with CAP, which found that antibiotic durations less than 5 days may be more beneficial than longer durations among patients who stabilize clinically by day 3 (12). However, unlike our current study, that trial did not assess mortality and had a limited sample size, limiting generalizability to real-world settings.

To better understand the effect of short-course therapy on real-world populations, we emulated a target trial using a 67-hospital cohort study of hospitalized, general care patients with CAP. We aimed to evaluate the percentage of hospitalized patients who would qualify for short therapy per the Pneumonia Short Treatment trial and the difference in 30-day clinical outcomes between patients who received a short

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versus longer course of antibiotics by emulating a target trial.

METHODS

Data Collection and Study Population

Patient data were obtained from the Hospital Medicine Safety Consortium (HMS), a statewide collaborative quality initiative sponsored by Blue Cross Blue Shield of Michigan and Blue Care Network. The HMS collects patient-level data on medical admissions, including clinical stability metrics, antibiotic prescriptions, and patient outcomes, through detailed medical record review conducted by trained nurse abstractors at participating hospitals (3, 13). Of the 92 eligible hospitals in Michigan, 67 (73%) participated in HMS during the study period.

Similar to previous HMS studies (3, 13), trained abstractors collected detailed data on eligible patients hospitalized for CAP. Patients eligible for HMS were those admitted to general care (that is, not intensive care) and discharged between 23 February 2017 and 31 July 2024 with a discharge diagnosis of CAP. Eligible patients received antibiotic therapy on hospital day 1 or 2.

The data collection method and quality assurance procedures of HMS have been previously described (3, 13). Briefly, trained abstractors entered data from the medical record into a central deidentified data set, which is checked for quality. Patient data, including demographic characteristics, daily vital signs, laboratory values, comorbid and concurrent conditions, antibiotic type and duration (including discharge prescriptions), and outcomes, were collected via the medical record through 30 days after hospitalization. To reduce the chance of missing outcomes if they occurred outside the electronic health record, patients were also called 30 days after discharge to collect additional data about posthospitalization outcomes (patients discharged to inpatient hospice, an extended care facility, or prison were ineligible for follow-up telephone calls).

This study received a status designation of not regulated, with a waiver for informed consent by the University of Michigan Medical School's Institutional Review Board. We followed the TARGET (TrAnsparent ReportinG of observational studies Emulating a Target trial) guideline (**Supplement Table 1**, available at Annals.org) (14).

Target Trial Specification

The target trial was designed to evaluate the effectiveness of shorter versus longer antibiotic treatment durations (15).

Eligibility Criteria

Similar to the Pneumonia Short Treatment trial, which reported the safety of a 3-day antibiotic duration for CAP (12), eligible patients had to have signs or symptoms and radiographic findings of pneumonia; had to have received 3 days of antibiotics while hospitalized; and had to achieve clinical stability by hospital day 3, defined as being afebrile (temperature ≤37.8 °C), with a heart rate less than 100 beats/min, respiratory rate less than 24 breaths/min, systolic blood pressure of 90 mm Hg or greater, arterial oxygen saturation of 90% or greater on room air or baseline oxygen, and normal mental status (12, 16). Similar to the Pneumonia Short Treatment trial, patients were excluded for the following reasons: severe underlying pulmonary disease, a pulmonary complication (for example, empyema), immunosuppression (for example, HIV, recent chemotherapy, congenital or acquired immunodeficiency, hematologic cancer, lymphoma, and asplenia), receipt of 2 or more days of empiric anti–methicillin-resistant *Staphylococcus aureus* or anti–*Pseudomonas aeruginosa* therapy (**Supplement**, available at Annals.org), *Legionella* or intracellular bacterial infection, end-stage renal failure, liver disease, β-lactam allergy, aspiration pneumonia, or no health care insurance (**Figure 1**).

Treatment Strategies

Eligible patients were assigned to 1 of 2 treatment strategies for subsequent antibiotic exposure: receipt of 0 or 1 additional days of antibiotic therapy (that is, short duration) or receipt of 2 or more additional days of antibiotic therapy (that is, longer duration). Antibiotics prescribed at discharge are included. We use the range of 0 to 1 days because HMS does not collect time stamps related to antibiotic prescribing, so 72 hours of therapy could be recorded as 3 or 4 days. For the same reason, treatment is considered stopped when a patient did not receive antibiotic treatment for 2 consecutive days.

Follow-up

For each eligible person, follow-up starts at assignment of treatment strategy (antibiotic day 3) and ends 30 days later.

Outcomes

The main outcome was all-cause mortality. Other outcomes included hospital readmission, urgent visits (including emergency department, observation admission, and urgent care visits), and *Clostridioides difficile* infection.

Causal Contrast

We estimated the per protocol effect defined as the difference between the average outcome that would have been observed if all patients had been adherent to short-duration therapy versus if all patients had been adherent to long-duration therapy (17).

Statistical Analysis

In the per protocol analysis of the target trial, the 30-day risks for the outcome can be calculated from the daily probability of the outcome estimated via pooled logistic regression with covariates treatment

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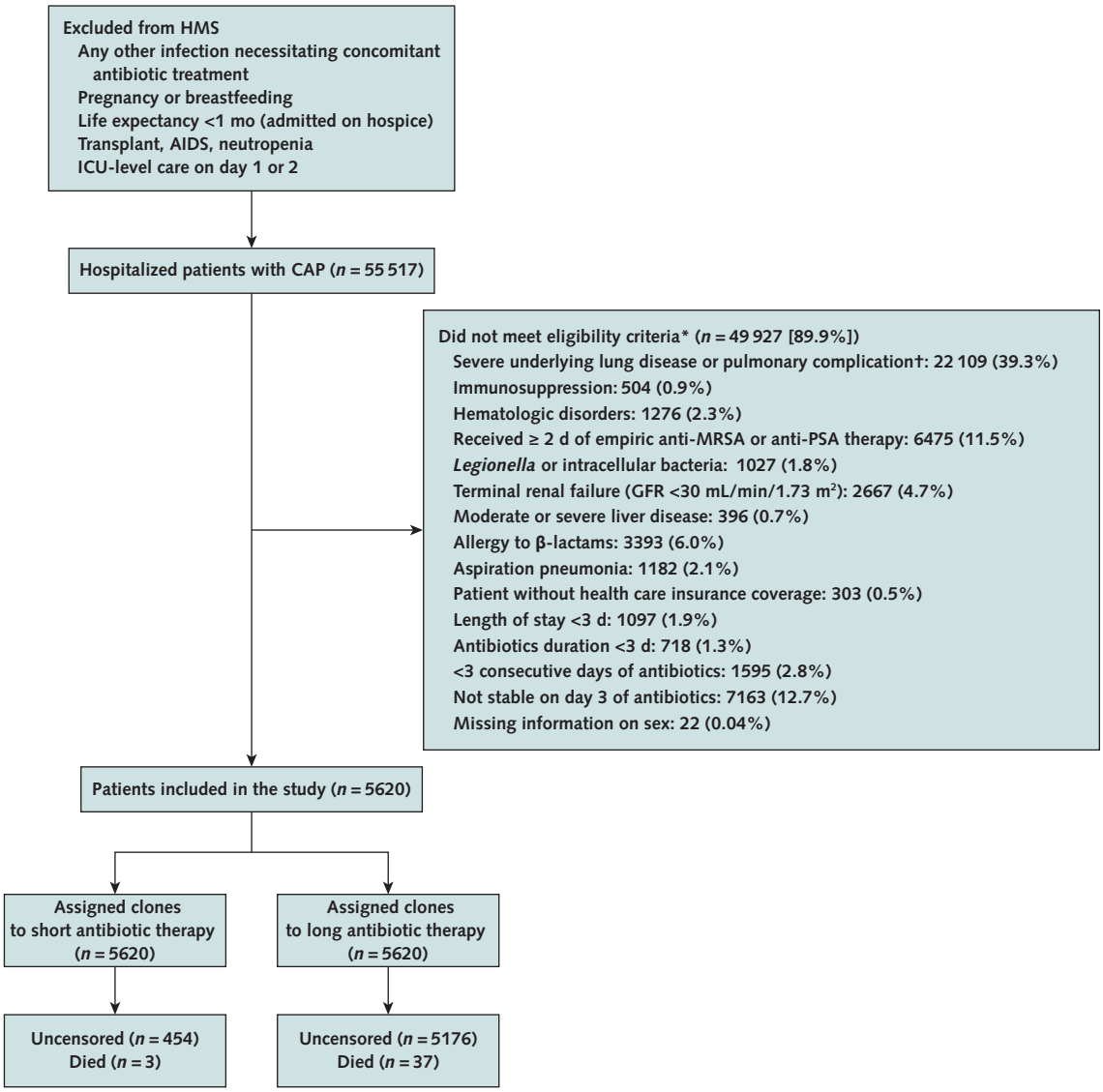
Figure 1. Study flow diagram.


Excluded from HMS
Any other infection necessitating concomitant antibiotic treatment
Pregnancy or breastfeeding
Life expectancy <1 mo (admitted on hospice)
Transplant, AIDS, neutropenia
ICU-level care on day 1 or 2
Hospitalized patients with CAP (n = 55 517)
Did not meet eligibility criteria* (n = 49 927 [89.9%])
Severe underlying lung disease or pulmonary complication†: 22 109 (39.3%)
Immunosuppression: 504 (0.9%)
Hematologic disorders: 1276 (2.3%)
Received ≥ 2 d of empiric anti-MRSA or anti-PSA therapy: 6475 (11.5%)
Legionella or intracellular bacteria: 1027 (1.8%)
Terminal renal failure (GFR <30 mL/min/1.73 m²): 2667 (4.7%)
Moderate or severe liver disease: 396 (0.7%)
Allergy to β-lactams: 3393 (6.0%)
Aspiration pneumonia: 1182 (2.1%)
Patient without health care insurance coverage: 303 (0.5%)
Length of stay <3 d: 1097 (1.9%)
Antibiotics duration <3 d: 718 (1.3%)
<3 consecutive days of antibiotics: 1595 (2.8%)
Not stable on day 3 of antibiotics: 7163 (12.7%)
Missing information on sex: 22 (0.04%)
Patients included in the study (n = 5620)
Assigned clones to short antibiotic therapy (n = 5620)
Assigned clones to long antibiotic therapy (n = 5620)
Uncensored (n = 454)
Died (n = 3)
Uncensored (n = 5176)
Died (n = 37)

CAP = community-acquired pneumonia; GFR = glomerular filtration rate; HMS = Hospital Medicine Safety Consortium; ICU = intensive care unit; MRSA = methicillin-resistant *Staphylococcus aureus*; PSA = *Pseudomonas aeruginosa*.

* Eligibility criteria based on exclusion criteria from the Pneumonia Short Treatment trial.

† Pulmonary complications (e.g., empyema), structural lung disease, severe chronic obstructive pulmonary disease, FEV_1 percentage predicted <80% and chronic obstructive pulmonary disease/emphysema, receiving home oxygen.

group indicator and day. Patients are censored if and when they deviate from their assigned treatment strategy, that is, when they stopped treatment early or when their treatment exceeded the short-duration limit. Because of potential selection bias introduced by this censoring, time-varying inverse probability weights can be used to adjust for baseline and time-varying risk factors.

In the observational emulation of the target trial, we followed the same analysis plan, with an exception. Because the treatment strategy was not known at baseline, we created 2 clones of eligible patients and assigned each clone to 1 of the strategies. Then the analysis was based on clones (**Supplement Figure**, available at Annals.org). Once the treatment strategy was known, this final weight was carried forward until the end of follow-up for the noncensored clones. If a clone became nonadherent after their final treatment strategy was known, they were censored at this point. This affected only 3 clones.

The denominator of the inverse probability weights was calculated from logistic regression models with random intercepts accounting for clustering at the hospital level; baseline covariates, including age, sex, race, ethnicity, smoking history, year of discharge, Charlson Comorbidity Index, individual comorbidities

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(congestive heart failure, chronic obstructive pulmonary disease, cancer, diabetes, cardiovascular disease, and chronic kidney or liver disease), skilled-nursing facility residence, CURB-65 score (Confusion, Urea nitrogen, Respiratory rate, Blood pressure, and age 65 years or older), Pneumonia Severity Index, and receipt of high-risk antibiotics before admission; and time-varying covariates updated daily, including vital sign abnormalities (heart rate, respiratory rate, systolic blood pressure, oxygen saturation, mental status, and fever). A complete list of covariates is provided in the **Supplement**. Because we do not have dates for when *C difficile* infection occurred, we used logistic regression (rather than pooled logistic regression models) with inverse probability weights based on the day treatment assignment was ascertained (the last weight, rather than daily inverse probability weights).

One hundred thirty-two patients were missing complete data on treatment duration due to the hospitals' data abstraction rules. These patients were reviewed on a case-by-case basis to determine their most likely antibiotic duration and grouped accordingly. These patients were categorized as follows: 5 days of inpatient treatment but unknown duration at discharge ($n = 32$; treated as long duration), 4 days of inpatient antibiotics and antibiotics prescribed for an unknown duration at discharge ($n = 30$; treated as long duration), 3 days of inpatient antibiotics and antibiotics prescribed at discharge for an unknown duration ($n = 59$; treated as long duration), treated with antibiotics until their transfer date ($n = 10$; uncensored in both treatment strategies), and treated with antibiotics for 4 days and transferred on day 5 ($n = 1$, treated as long duration). The only missing data were for 22 patients (0.4%) who lacked sex information and were excluded.

We reviewed patients with a short antibiotic duration who had adverse events from antibiotic therapy within the first 5 days of hospitalization, and all of them had alternative antibiotics that could have been prescribed, suggesting that the short duration was purposeful rather than due to an adverse effect. We used a sensitivity analysis excluding patients who received antibiotics before admission to evaluate the robustness of the results. We provide all model results as absolute risk by group as well as risk ratios with 95% CI. For the pooled logistic models, the 95% CIs were calculated via bias-corrected bootstrap intervals (18). Statistical analyses were done using SAS, version 9.4 (SAS Institute).

Role of the Funding Source

The funding source had no role in the design, conduct, analysis, or reporting of the study.

RESULTS

Patient Characteristics

After the exclusion criteria from the Pneumonia Short Treatment trial (12) were applied, only 10.1% (5620 patients across 67 hospitals) of patients qualified for the trial (study flow diagram in **Figure 1**).

Of the 5620 eligible patients, 54.3% were men, with a median age of 68.2 years (**Table 1**). At admission, most patients were identified as White (71.6%). The median Charlson Comorbidity Index was 2 (IQR, 1 to 3) and the median CURB-65 score was 2 (IQR, 1 to 3), indicating moderate severity of illness. Only 4.4% ($n = 249$) of patients received a 3-day antibiotic duration; 3.5% ($n = 195$) received a 4-day duration. The percentage who received a short duration (3 to 4 days) was 5% to 7% in 2017 to 2020 and 9% to 11% in 2022 to 2024 and varied across hospitals from 0% to 18.2% (median, 7.5%), with 3 of 67 hospitals contributing no short-duration patients.

Microbiology and Antibiotics in Included Patients

The median total antibiotic duration of all patients eligible for a short duration was 7 days (IQR, 5 to 8 days), of whom most received empiric ceftriaxone (89.3%, $n = 5016$) or azithromycin (76.9%, $n = 4319$). Azithromycin (34.2%, 1554 of 4540), amoxicillin–clavulanate (19.9%, 905 of 4540), and oral cephalosporins (39.4%, 1788 of 4540) were the most frequently prescribed discharge antibiotics (**Table 1**). The viral positivity rate was 6.3% for short duration and 4.7% for longer duration (risk difference, 1.6 percentage points [95% CI, 0.7 to 4.0 percentage points]).

Outcomes

Of the 5620 eligible patients, 11 240 clones were created and assigned to the short- and longer-duration groups. During follow-up, 5166 clones (91.9%) in the short-duration group were censored after exceeding 4 days of antibiotic therapy and 444 clones (7.9%) in the longer-duration group were censored due to early discontinuation before day 5. Twenty clones (10 patients [0.2%]) remained uncensored in both groups through the end of follow-up.

Three (0.7%) deaths occurred in the short-duration group, and 37 (0.7%) deaths occurred in the longer-duration group, with median time to death of 21 days (IQR, 1 to 29 days) and 18 days (IQR, 14 to 23 days), respectively (**Figure 2**). The unadjusted 30-day risk ratio of mortality for short- versus longer-duration antibiotic therapy was 0.92 (CI, 0.01 to 2.38) and, after adjustment, the risk ratio was 0.89 (CI, 0.01 to 2.25) (**Table 2**).

In the short-duration group, 40 (8.8%) readmissions were observed within 30 days, whereas the longer-duration group had 417 (8.1%) readmissions. Regarding urgent visits, the short-duration group had 37 (8.1%) versus 458 (8.8%) for the longer-duration group. One (0.2%) *C difficile* infection occurred in the short-duration group, and 11 (0.2%) occurred in the longer-duration group. For short- versus longer-duration antibiotic therapy, unadjusted 30-day risk ratios were 1.10 (CI, 0.82 to 1.43) for readmission, 0.91 (CI,

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Table 1. Characteristics of Patients Eligible for a Three-Day Duration ($n = 5620$ Patients, 67 Hospitals)

Variable	Eligible for Target Trial ($n = 5620$)
Sex, *n* (%)	
Female	2569 (45.7)
Male	3051 (54.3)
Median age (IQR), *y*	68.2 (56.1–80.0)
Race, *n* (%)	
Black or African American	1297 (23.1)
White	4025 (71.6)
Asian	35 (0.6)
Other*	146 (2.6)
Unknown*	117 (2.1)
Ethnicity, *n* (%)	
Non-Hispanic	4848 (86.3)
Hispanic	111 (2.0)
Unknown*	661 (11.8)
Skilled-nursing facility before hospitalization, *n* (%)	202 (3.6)
Median Charlson Comorbidity Index score (IQR)	2 (1–3)
Comorbidities, *n* (%)	
Congestive heart failure	1248 (22.2)
Mild COPD	1688 (29.9)
Cancer	812 (14.4)
Diabetes mellitus	1569 (27.9)
Cardiovascular disease	2286 (40.7)
Moderate or severe chronic kidney disease	1216 (21.6)
Moderate or severe liver disease	220 (3.9)
Smoking history, *n* (%)	
Never	2151 (38.3)
Former	1926 (34.3)
Current/active	1460 (26.0)
Unknown	83 (1.5)
Year of discharge, *n* (%)	
2017	648 (11.5)
2018	696 (12.4)
2019	742 (13.2)
2020	461 (8.2)
2021	690 (12.3)
2022	857 (15.2)
2023	1027 (18.3)
2024	499 (8.9)
Cough, *n* (%)	4701 (83.6)
Dyspnea, *n* (%)	4215 (75.0)
Increased sputum, *n* (%)	2508 (44.6)
Chills, *n* (%)	1934 (34.4)
Egophony, *n* (%)	18 (0.3%)
Rales, *n* (%)	855 (15.2)
Bronchial breath sounds, *n* (%)	19 (0.3)
Rhonchi, *n* (%)	1612 (28.7)
Dullness of percussion, *n* (%)	12 (0.2)
Crackles, *n* (%)	1340 (23.8)
Median CURB-65 score (IQR)†	2 (1–3)
Received high-risk antibiotic in prior 90 d, *n* (%)§	625 (11.1)
Tachypnea (respiratory rate >20 breaths/min), *n* (%)	3393 (60.4)
Leukocytosis (leukocyte count >10 × 10^9 cells/L), *n* (%)	3572 (63.6)
Abnormal temperature (>38 or <36 °C), *n* (%)	1603 (28.5)
Hypoxemia (oxygen saturation <90%), *n* (%)	1354 (24.1)
Leukopenia (leukocyte count <4 × 10^9 cells/L), *n* (%)	214 (3.8)
Positive respiratory culture in 90 d before hospitalization, *n* (%)	6 (0.1)
Respiratory or blood culture, *n* (%)	
Not performed	1272 (22.6)
Negative	4097 (72.9)
Positive (non–multidrug-resistant organism)	200 (3.6)
Positive (multidrug-resistant organism)	51 (0.9)
Have chest radiograph, *n* (%)	5313 (94.5)
Have several chest radiographs, *n* (%)	957 (17.0)
Have chest computed tomography, *n* (%)	2705 (48.1)
Median Pneumonia Severity Index (IQR)‡	87.2 (67.4–109.2)

Continued on next column

Table 1–Continued

Variable	Eligible for Target Trial ($n = 5620$)
Pneumonia Severity Index, *n* (%)‡	
Class I: <50	619 (11.0)
Class II: 51–70	982 (17.5)
Class III: 71–90	1406 (25.0)
Class IV: 91–130	2034 (36.2)
Class V: >130	579 (10.3)
Exacerbation of COPD, *n* (%)	855 (15.2)
Exacerbation of congestive heart failure, *n* (%)	399 (7.1)
Median time to clinical stability (IQR), *d*‖	3 (2–3)
Median length of stay (IQR), *d*	4 (3–5)
Respiratory culture or nonculture test, *n* (%)	
Not performed	2554 (45.4)
Negative	2880 (51.2)
Any positive	186 (3.3)
Initial procalcitonin, *n* (%)	
Not performed	3373 (60.0)
0–0.1 ng/mL	983 (17.5)
0.1–0.25 ng/mL	484 (8.6)
0.25–0.5 ng/mL	240 (4.3)
>0.5 ng/mL	540 (9.6)
Median total antibiotic duration (IQR), *d*	7 (5–8)
Empiric antibiotic agent (hospital day 1 or 2), *n* (%)	
Ceftriaxone	5016 (89.3)
Azithromycin	4319 (76.9)
Levofloxacin	295 (5.2)
Doxycycline	1321 (23.5)
Vancomycin	202 (3.6)
Cefepime	149 (2.7)
Piperacillin–tazobactam	89 (1.6)
Ampicillin–sulbactam	352 (6.3)
Metronidazole	87 (1.5)
Moxifloxacin	35 (0.6)
Ciprofloxacin	5 (0.09)
Other	203 (3.6)
Discharge to skilled-nursing facility, *n* (%)	432 (7.7)
Newly discharged to skilled-nursing facility (i.e., not admitted from skilled-nursing facility), *n* (%)	326 (5.8)
Discharged on antibiotics, *n* (%)	4540 (80.8)
Median discharge antibiotic duration (IQR), *d*	3 (2–5)/4 (2–5)¶
Oral antibiotic agent prescribed on discharge, *n* (%)	
Azithromycin	1554 (34.2)
Oral cephalosporin	1788 (39.4)
Levofloxacin	582 (12.8)
Amoxicillin–clavulanate	905 (19.9)
Doxycycline	875 (19.3)
Moxifloxacin	145 (3.2)
Penicillin/amoxicillin	85 (1.9)
Metronidazole	16 (0.4)
Ciprofloxacin	19 (0.4)

COPD = chronic obstructive pulmonary disease; CURB-65 = Confusion, Urea nitrogen, Respiratory rate, Blood pressure, and age ≥65 years.

* Other race includes American Indian or Alaskan Native, Arab and Chaldean Ancestries, Native Hawaiian or Pacific Islander, and any other race not including any of the above. Unknown race and ethnicity indicates that the patient's race and ethnicity was not indicated in the medical record.

† Includes confusion, blood urea nitrogen >7 mmol/L (>19 mg/dL), respiratory rate ≥30 breaths/min, systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg, and age ≥65 y. Higher scores indicate more severe disease.

‡ Includes age, sex, comorbidities, vital sign and laboratory abnormalities, and pleural effusion on imaging. Higher scores indicate more severe disease.

§ Includes any intravenous antibiotic, any fluoroquinolone, or linezolid, given that these are associated with increased risk for multidrug-resistant organisms or are active against methicillin-resistant *Staphylococcus aureus* or *Pseudomonas* species.

‖ Defined as afebrile (temperature ≤37.8 °C), heart rate <100 beats/min, respiratory rate <24 breaths/min, systolic blood pressure ≥90 mm Hg, oxygen saturation ≥90% on room air or baseline oxygen, and normal mental status.

¶ All patients/duration for those who received antibiotics at discharge.

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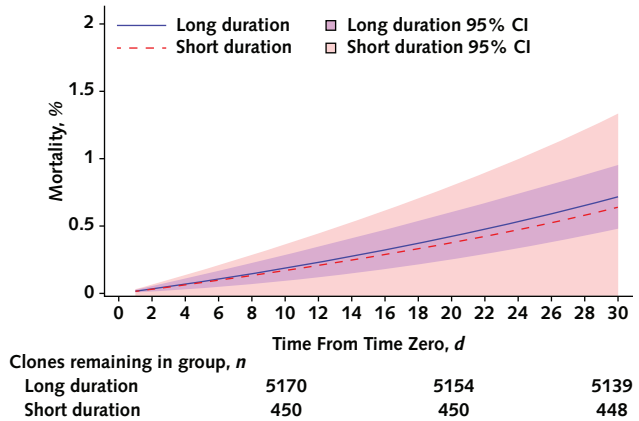
Figure 2. Mortality in patients with CAP treated with short-duration versus longer-duration antibiotic treatment.



Numbers refer to clones remaining in each group on days 10, 20, and 30, respectively. CAP = community-acquired pneumonia.

0.68 to 1.25) for urgent visits, and 1.08 (CI, 0.19 to 6.25) for *C difficile* infection. The adjusted 30-day risk ratios for readmission, urgent visit, and *C difficile* infection in short- versus longer-duration antibiotic therapy were 1.07 (CI, 0.81 to 1.42), 0.94 (CI, 0.70 to 1.28), and 1.01 (CI, 0.18 to 5.68), respectively (**Table 2**).

Antibiotic-associated adverse events occurred in 131 (2.3%) patients: 15 (3.3%) in the short-duration group and 116 (2.2%) in the longer-duration group. The physician-reported adverse events occurred in 77 (1.4%) patients: 13 (2.9%) in the short-duration group and 64 (1.2%) in the longer-duration group. The most common adverse events in both groups were diarrhea, rash, and renal failure.

Sensitivity analyses showed no change in the effect estimates after excluding patients who received antibiotics before admission (**Supplement Table 2**, available at Annals.org).

DISCUSSION

We emulated a target trial of 5620 patients with CAP who were admitted to 67 hospitals and stabilized by day 3 to compare outcomes for those receiving 0 to 1 additional days of antibiotic treatment versus those receiving 2 or more days of additional antibiotic treatment (that is, shorter [3 to 4 days] vs. longer [≥5 days] total antibiotic duration). Only 10% of our initial general care CAP population was eligible for our target trial based on the Pneumonia Short Treatment trial criteria. Among eligible patients, short antibiotic duration was uncommon (less than 8%), although its use increased modestly over time and varied widely across hospitals. All outcomes, including mortality, readmission, urgent visits, *C difficile* infection, and adverse events, were infrequent and similar between groups. However, given the imprecision of the estimates, our results are compatible with both benefit and harm according to conventional statistical criteria.

We found few patients who were eligible for a short (3- to 4-day) duration, mostly due to exclusions for underlying comorbidities. Strict eligibility criteria can compromise the generalizability of trial findings to real-world clinical practice. For example, a systematic review reported that treatment trials for physical conditions often exclude many patients who have the condition treated in the trial, with 4 out of 5 trials excluding at least half of the potential patients (19). Except for patients who develop severe complications (for example, empyema) or have multidrug-resistant organisms identified, no trials to our knowledge have found that longer durations of antibiotic therapy are safer for patients with comorbidities or those who do not meet clinical stability criteria. Thus, it is unclear what duration is safest for the 90% of patients who would be excluded from this trial.

Our results are most applicable to non–intensive care unit adults who are hospitalized with CAP and clinically stable after 3 days of hospital care. These patients were admitted to general care without severe extrapulmonary infections or critical illness and did not have confirmed or suspected COVID-19. Clinical stability was defined as being afebrile, having no new or increased supplemental oxygen, having stable vital signs (that is, no hypotension, tachycardia, or new mental status changes), and having no escalation of antibiotic therapy on hospital day 3. In addition, our cohort had a median CURB-65 score of 2, indicating that many participants might have been eligible for outpatient management per initial CURB-65 guidance; thus, our findings likely apply to patients on the milder end of the clinical spectrum. Currently, the American Thoracic Society and Infectious Diseases Society of America guidelines for treatment of CAP in hospitalized patients recommend using measures of clinical stability to determine the duration of treatment (11, 20). This includes the resolution of vital sign abnormalities, ability to eat, and normal mentation. The findings from our study support these recommendations.

In addition to the Pneumonia Short Treatment trial (12), a systematic review and meta-analysis offers support for the noninferiority of shorter treatment (3 to 5 days) compared with 10-day treatments of CAP in clinically stable adults (22). Other observational studies suggest that shorter antibiotic therapy is associated with lower rates of antimicrobial resistance to respiratory pathogens because of shorter selection pressure for multidrug-resistant organisms (23); lower risk for adverse effects in patients hospitalized with CAP (3); cost savings, both for the health care system and the patient, due to decreased resource use (23); and improved adherence to therapy (24). Overall, these benefits offer valuable support for adopting short-course therapy for CAP in stabilized patients who have been hospitalized.

Our study has limitations. Our causal inferences rely on the assumption of no selection bias after censoring, which may not be true if such factors as patient

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Table 2. Risk Differences in Outcomes in Persons Receiving Shorter Antibiotic Treatment Duration Compared With Longer Antibiotic Treatment Duration*

30-Day Postrandomization Outcomes	Short Duration ($n = 454$), %	Long Duration ($n = 5176$), %	Adjusted Risk Ratio (95% CI)†
Mortality	0.65 (0.00–1.46)	0.73 (0.53–1.01)	0.89 (0.01–2.25)
Readmission	8.80 (6.86–11.88)	8.21 (7.76–9.01)	1.07 (0.81–1.42)
Urgent visit‡	8.39 (6.17–10.97)	8.90 (8.16–9.64)	0.94 (0.70–1.28)
Clostridioides difficile infection	0.06 (0.01–0.36)	0.06 (0.01–0.27)	1.01 (0.18–5.68)

* $n = 5630$ is the analytic cohort (uncensored clones).
† Adjusted risk ratios are presented for the effect of antibiotic treatment duration (shorter vs. longer) on 30-day postrandomization mortality, readmission, and urgent visits. Adjusted risk ratios were derived from a weighted pooled logistic regression model, incorporating stabilized inverse probability of censoring weights to account for hospital clustering, baseline covariates, and time-varying clinical stability metrics. All non–time-varying covariates are included in Table 1. Time-varying (daily) covariates include abnormal heart rate, respiratory rate, systolic blood pressure, oxygen saturation, altered mental status, and fever. Adjusted risk ratio is shown for *C difficile* infection; weighting and adjustments are the same for this outcome. Weights were calculated daily until treatment strategy was determined, as described in the Methods.
‡ Includes any urgent visit not resulting in hospitalization, including emergency department visit, urgent care visit, or observation stay.

antibiotic adherence, socioeconomic status, or clinician treatment preference (which were not adjusted for) were confounders. The small sample of patients with short-duration antibiotic therapy and low mortality rate for all patients reduced our ability to precisely estimate the risks. The study's 30-day follow-up period precludes assessment of longer-term outcomes, and we excluded certain patients (those discharged to hospice, an extended care facility, or prison) from asking about adverse events. Finally, clinical stability criteria may not fully identify higher-risk elderly patients who can present with atypical or subtle signs of illness (25).

This study has several notable strengths. By using a target trial framework, we reduced common sources of bias seen in observational studies, including immortal time bias (15, 26). Our use of inverse probability weighting allowed for appropriate adjustment for time-varying confounders. Finally, our study's large, multicenter cohort across 67 hospitals enhances the generalizability of findings to real-world practice.

Our study has identified some critical research questions. Given that 90% of patients were excluded, we need additional pragmatic, real-world data on the safety and efficacy of shorter antibiotic courses in higher-risk patients, such as those with more severe CAP, immunosuppression, multiple comorbidities, or persistent vital sign abnormalities. Incorporating patient-reported outcomes (27), including quality of life, antibiotic-associated adverse events, and symptom resolution, would provide a more comprehensive evaluation of treatment strategies given low overall mortality.

In conclusion, only 10.1% of inpatients with CAP met the strict eligibility criteria for short-course therapy. In this subset, mortality was very low in both duration groups, and there were no differences observed in other outcomes between short and long duration.

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References

1. **Ramirez JA, Wiemken TL, Peyrani P, et al; University of Louisville Pneumonia Study Group.** Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. Clin Infect Dis. 2017;65:1806-1812. [PMID: 29020164] doi:10.1093/cid/cix647
2. **Tamma PD, Avdic E, Li DX, et al.** Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med. 2017; 177:1308-1315. [PMID: 28604925] doi:10.1001/jamainternmed.2017.1938

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3. **Vaughn VM, Flanders SA, Snyder A, et al.** Excess antibiotic treatment duration and adverse events in patients hospitalized with pneumonia. A multihospital cohort study. Ann Intern Med. 2019;171:153-163. [PMID: 31284301] doi:10.7326/M18-3640
4. **Kazakova SV, Baggs J, McDonald LC, et al.** Association between antibiotic use and hospital-onset *Clostridioides difficile* infection in US acute care hospitals, 2006-2012: an ecologic analysis. Clin Infect Dis. 2020;70:11-18. [PMID: 30820545] doi:10.1093/cid/ciz169
5. **Centers for Disease Control and Prevention.** Antibiotic Resistance Threats in the United States. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2019. doi:10.15620/cdc:82532
6. **Madaras-Kelly KJ, Burk M, Caplinger C, et al; Pneumonia Duration of Therapy Medication Utilization Evaluation Group.** Total duration of antimicrobial therapy in veterans hospitalized with uncomplicated pneumonia: results of a national medication utilization evaluation. J Hosp Med. 2016;11:832-839. [PMID: 27527659] doi:10.1002/jhm.2648
7. **Haas MK, Dalton K, Knepper BC, et al.** Effects of a syndrome-specific antibiotic stewardship intervention for inpatient community-acquired pneumonia. Open Forum Infect Dis. 2016;3:ofw186. [PMID: 27747254] doi:10.1093/ofid/ofw186
8. **Schuler CL, Courter JD, Conneely SE, et al.** Decreasing duration of antibiotic prescribing for uncomplicated skin and soft tissue infections. Pediatrics. 2016;137:e20151223. [PMID: 26783327] doi:10.1542/peds.2015-1223
9. **Avdic E, Cushinotto LA, Hughes AH, et al.** Impact of an antimicrobial stewardship intervention on shortening the duration of therapy for community-acquired pneumonia. Clin Infect Dis. 2012;54:1581-1587. [PMID: 22495073] doi:10.1093/cid/cis242
10. **Li JZ, Winston LG, Moore DH, et al.** Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. Am J Med. 2007;120:783-790. [PMID: 17765048] doi:10.1016/j.amjmed.2007.04.023
11. **Jones BE, Ramirez JA, Oren E, et al; American Thoracic Society Assembly on Pulmonary Infections and Tuberculosis.** Diagnosis and management of community-acquired pneumonia: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2026;212:24-44. [PMID: 40679934] doi:10.1164/rccm.202507-1692ST
12. **Dinh A, Ropers J, Duran C, et al; Pneumonia Short Treatment (PTC) Study Group.** Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial. Lancet. 2021;397:1195-1203. [PMID: 33773631] doi:10.1016/S0140-6736(21)00313-5
13. **Vaughn VM, Gandhi TN, Hofer TP, et al.** A statewide collaborative quality initiative to improve antibiotic duration and outcomes in patients hospitalized with uncomplicated community-acquired pneumonia. Clin Infect Dis. 2022;75:460-467. [PMID: 34791085] doi:10.1093/cid/ciab950
14. **Cashin AG, Hansford HJ, Hernán MA, et al.** Transparent Reporting of Observational Studies Emulating a Target Trial—the TARGET statement. JAMA. 2025;334:1084-1093. [PMID: 40899949] doi:10.1001/jama.2025.13350
15. **Hernán MA, Wang W, Leaf DE.** Target trial emulation: a framework for causal inference from observational data. JAMA. 2022;328:2446-2447. [PMID: 36508210] doi:10.1001/jama.2022.21383
16. **Mandell LA, Wunderink RG, Anzueto A, et al; American Thoracic Society.** Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44 Suppl 2: S27-S72. [PMID: 17278083] doi:10.1086/511159
17. **Hernán MA, Hernández-Díaz S.** Beyond the intention-to-treat in comparative effectiveness research. Clin Trials. 2012;9:48-55. [PMID: 21948059] doi:10.1177/1740774511420743
18. **Martinez WL, Martinez AR**. Computational Statistics Handbook with MATLAB. CRC Pr; 2001.
19. **He J, Morales DR, Guthrie B.** Exclusion rates in randomized controlled trials of treatments for physical conditions: a systematic review. Trials. 2020;21:228. [PMID: 32102686] doi:10.1186/s13063-020-4139-0
20. **Metlay JP, Waterer GW, Long AC, et al.** Diagnosis and treatment of adults with community-acquired pneumonia. an official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200:e45-e67. [PMID: 31573350] doi:10.1164/rccm.201908-1581ST
21. **el Moussaoui R, de Borgie CAJM, van den Broek P, et al.** Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ. 2006;332:1355. [PMID: 16763247] doi:10.1136/bmj.332.7554.1355
22. **Furukawa Y, Luo Y, Funada S, et al.** Optimal duration of antibiotic treatment for community-acquired pneumonia in adults: a systematic review and duration-effect meta-analysis. BMJ Open. 2023;13: e061023. [PMID: 36948555] doi:10.1136/bmjopen-2022-061023
23. **Llor C, Frimodt-Møller N, Miravitlles M, et al.** Optimising antibiotic exposure by customising the duration of treatment for respiratory tract infections based on patient needs in primary care. EClinicalMedicine. 2024;74:102723. [PMID: 39070175] doi:10.1016/j.eclinm.2024.102723
24. **Kardas P.** Patient compliance with antibiotic treatment for respiratory tract infections. J Antimicrob Chemother. 2002;49:897-903. [PMID: 12039881] doi:10.1093/jac/dkf046
25. **Metlay JP, Atlas SJ, Borowsky LH, et al.** Time course of symptom resolution in patients with community-acquired pneumonia. Respir Med. 1998;92:1137-1142. [PMID: 9926169] doi:10.1016/s0954-6111(98)90408-5
26. **McDonald EG, Prosty C, Hanula R, et al.** Observational versus randomized controlled trials to inform antibiotic treatment durations: a narrative review. Clin Microbiol Infect. 2023;29:165-170. [PMID: 36108947] doi:10.1016/j.cmi.2022.09.002
27. **Finer E, Pulia MS, Harrison JD, et al.** A desirability of outcome ranking for adults with non-severe community-acquired pneumonia: a comparison of physician and patient preferences. Antimicrob Steward Healthc Epidemiol. 2025;5:e282. [PMID: 41180299] doi:10.1017/ash.2025.10195

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